

Human Papilloma Virus: Combatting Cancer with Vaccination

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SUMMARY

Human papilloma virus (HPV) is a virus responsible for cancer progression, and it has been directly associated with the development of cervical cancer. HPV-positive tumours have also been found in oral cavities, creating a rise in head and neck cancers. Recently, a vaccine has been developed that is highly effective at preventing the pathogenesis of HPV and HPV-related cancers. This article reviews the basic progression of HPV in the body and expands on the newfound dangers associated with this prevalent sexually transmitted disease.

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INTRODUCTION

Human papilloma virus (HPV) is the most common chronic sexually transmitted disease (Workowski and Berman, 2010). This can be attributed to HPV's ability to transmit through condoms, while producing few symptoms in the host (Watson, 2005). In severe cases, those infected with HPV can develop high-risk cancers, such as cervical cancer (Burd, 2003). Due to the disease's widespread prevalence, public health experts produced a vaccine that immunizes for two of the most prevalent high-risk (HR) strains of HPV; HPV-16 and HPV-18 (National Cancer Institute, 2016). This vaccine was originally advertised for preteen girls, who are less likely to be sexually active (National Cancer Institute, 2016) thus reducing their exposure to HPV and subsequent risk of cervical cancer. The most current vaccine covers nine of over a dozen HR strains of HPV (National Cancer Institute, 2016).

During the years 2007 to 2012, Canada only vaccinated young girls, as HR HPVs are directly associated with the development of cervical cancer (Public Health Agency of Canada, 2015). The recent decrease in cervical cancer has been attributed to the effectiveness of the vaccine

(Brotherton, et al., 2011). Interestingly, a steady increase in head and neck cancers has been reported, especially in unvaccinated HPV positive individuals (Kimple and Harari, 2015). These tumours are prominent in males; however, women can also have HPV positive oral tumours. It is hypothesized that this increase of head and neck cancers is associated with modern sexual attitudes, including the increase of oral sex performed on partners (Marur, D'Souza, Westra and Forastiere, 2010). As both the vaginal tract and the oral cavity are lined by mucosal cells, for which HPV is tropic, the virus can be easily spread between the female genital tract and the oral cavity, providing optimal conditions for potential cancer development. This paper aims to present a comprehensive overview of HPV, including its virology, cancer pathogenesis, and the importance of vaccination.

HPV STRUCTURE

HPV is a small (50-60 nm diameter) virus that consists of a genome of 8000 base pairs (Figure 1) (Doorbar et al., 2015). This encodes for the viral proteins that are required for both viral spreading and invasion. The virus encodes for both capsid proteins and virulent proteins that are responsible for the structural integrity and pathogenesis of

the virus, respectively. The capsid proteins include L1 and L2. Meanwhile, the E2 protein acts as a regulator for the expression of viral

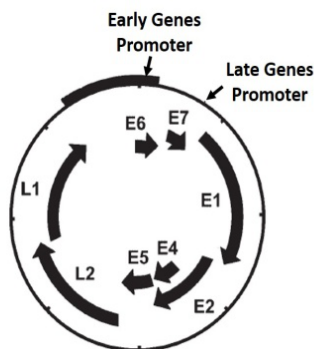
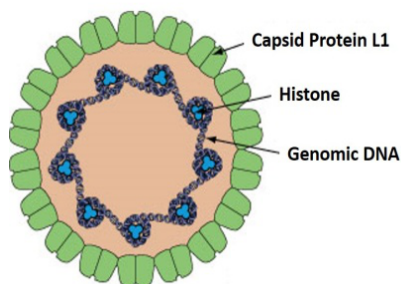


Figure 1: The structure of HPV. The image on the left shows the structure of the virion with the main capsid protein L1. The image on the right shows the genome organization of HPV. The most important proteins for viral pathogenesis are the early genes, E6 and E7; their regulator, E2; and the late capsid proteins, L1 and L2 (Hebner and Laimins, 2006).

proteins downstream of itself in the genome, particularly E6 and E7. The E6 and E7 proteins are essential for establishing an infection and immune evasion.

INITIAL INFECTION

HPV can be classified as either low risk (LR) or HR, where LR HPVs result in non-cancerous genital warts and HR HPVs can result in either warts or gradually develop into cancer within the cervix or oral cavity (Münger, et al., 2004). This difference in pathogenesis is due to a decreased effectiveness of E6 and E7 in the LR strains (Münger et al., 2004). Both LR and HR HPVs progress identically through the mucosal layers (Figure 2). Infection initiates at the basal layer of the skin, and progresses to the spinosum layer (Longworth and Laimins, 2004). At this point, the virus enters neighbouring cells. The infection continues, passing through the upper layers of the skin – the granulosum layer and corneum layer. At this stage, uninfected cells would come out of the cell cycle to become keratin-filled sacs that make up the top layer of skin. However, the E7 protein of HPV is able to alter P21, a key cell cycle regulating protein, causing the infected cell to remain in the cell cycle. This ensures that the cellular replication machinery remains functional to continue to replicate the viral genome.

CHRONIC INFECTION

In most cases, the host is able to clear the virus using both the innate and adaptive immune pathways (Scott, et al., 2013). Clearance occurs within the first six months of being infected for 80-90% of individuals; however, during this time

the virus can still be spread from the infected individual (Molano, et al., 2003). LR HPVs are more likely to be cleared in this time, with HR

HPV infections taking up to one year to be cleared. However, if the virus successfully evades the host's immune system, it can eventually progress to a chronic infection for the remaining 10-20% of individuals. It is these individuals that risk developing cancer (Burd, 2003).

Once a chronic infection is established, one of the main factors that determines the development of cancer is the random integration of the viral genome into the host's genome (Williams, Filippova, Soto and Duerksen-Hughes, 2011). The viral genetic information is typically integrated in common fragile sites of the host's chromosomes, which are found in every individual (Thorland, Myers, Gostout and Smith, 2003; Williams, et al., 2011). When integration occurs, the viral genome is cleaved at the E2 gene. The downstream E6 and E7 genes are then integrated into the host. Since E2 is a regulator of E6 and E7, their expression is no longer controlled in the host chromosome, resulting in their overexpression. These proteins, particularly E7, are responsible for keeping the cell in its replicative cycle. When they are overexpressed, this can lead to uncontrolled cell growth and cell immortalization, which are hallmarks of cancer.

Integration into the host genome does not guarantee the development of cancer as the host can still combat the effects of chromosome integration. Those who develop cancer typically have environmental co-factors that make the cell more likely to become cancerous (Wang, et al., 2009). These co-factors include smoking, drinking, and hormonal birth control use. Each

of these factors can directly change the mucosal cell environment in either the cervix or the oral cavity.

HPV-SPECIFIC CANCER PROGRESSION

In an HPV transfection study on human epithelial cells, E6 and E7 were shown to be directly involved in the transformation of these cells into malignant cancers. Hawley-Nelson, et al. (1989) created a plasmid consisting of the genome segments for E6 and E7. They placed transcription termination sequences at E6, E7, or both segments to prevent the translation of these proteins. When E7 was inhibited, no proliferative cell activity was observed. When E6 was inhibited, there was some proliferation, however at a slower rate than the positive control group. In addition, senescence was observed after two months of observation. When both E6 and E7 were permitted for transcription, proliferation continued for several months with no sign of senescence. This experiment supported the importance of E6, and particularly E7, in transforming infected cells (Hawley-Nelson, et al., 1989).

E6 and E7 are critical to the cancer progression associated with HPV integration as both can create complexes within cells that inhibit natural

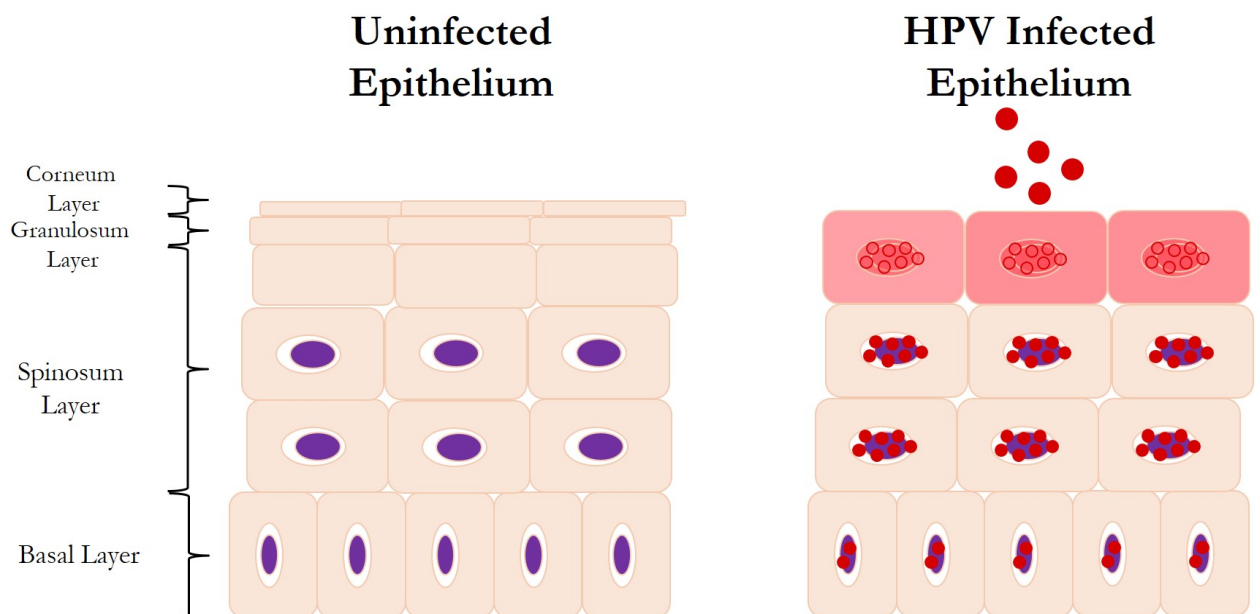
cell cycle regulation checkpoints (Münger, et al., 2004). For instance, E6-mediated viral pathways can result in the degradation of p53, a protein involved in cell cycle checkpoints (Bernard, et al., 2011; Münger, et al., 2004). E6 can also create binding complexes that allow for HPV-infected daughter cells to have never-ending telomerase, a genome sequence that signals for cell death when it is used up, resulting in the evasion of apoptosis (Oh, Kyo and Laimins, 2001).

E7 is arguably more pathogenic than E6, as it typically increases the rate of E6 reactions and initiates its own cellular pathways (Yim and Park, 2005; Münger, et al., 2004). E7 can inhibit the function of the Retinoblastoma protein (pRB), allowing cells to enter the S1 phase of the cell cycle without regulation, bypassing a major cell cycle checkpoint. The manipulation of these pathways by viral E6 and E7 results in uncontrolled proliferation of HPV infected cells, resulting in tumour formation.

PUBLIC HEALTH CONSIDERATIONS

In 2007, the annual financial burden of HPV was \$300 million, with nearly 18% of this cost coming from the treatment of genital warts and cervical cancer (Lalonde, 2007). The quadrivalent recombinant vaccine covering HPV 6, 11, 16,

Figure 1: Comparison between uninfected and infected epithelium upon initial infection by HPV. HPV enters the basal layer through microabrasions. From here it establishes a low resident viral load that is passed on when the basal cell divides. HPV then moves through the layers of the skin as the epithelial cells continue to divide. Figure modified from (Longworth and Laimins, 2004).



and 18 is a strong solution to reduce the financial burden while improving public health. A fully efficacious vaccine administered to 12-year-old Canadian girls would prevent nearly 10,000 cases of genital warts and 140 cases of cervical cancer per 100,000 vaccinations. In addition, the estimated disease-associated cost savings would amount to \$7.7 million per 100,000 vaccinations, which can greatly influence healthcare spending towards other, non-preventable illnesses (Lalonde, 2007). Recently, these vaccines have become available to males as well in hopes of decreasing the current rates of HPV positive oral cancers. It is critical to vaccinate for HPV, as vaccination costs less than cancer treatment and because it can prevent future suffering of HPV-positive cancers, whether they are cervical or head and neck related.

CONCLUSIONS

Due to the obvious effectiveness of the HPV vaccine, it is recommended by Health Canada that vaccination of non-sexually active pre-teen females and males be continued across the nation. As HPV-related cancers are attributed to great health and financial burdens, preventing the spread and development of HR HPVs is crucial to the population. Now that researchers understand the pathogenicity of the HPV virus, more effective vaccines can be produced that allow for the at-risk population to be immunized against HR and potentially LR HPV types.

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